

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number
WO 2004/028423 A1

(51) International Patent Classification⁷: **A61F 13/00**

(21) International Application Number:
PCT/GB2003/004118

(22) International Filing Date:
25 September 2003 (25.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0222527.4 27 September 2002 (27.09.2002) GB
60/486,445 14 July 2003 (14.07.2003) GB

(71) Applicant (*for all designated States except US*): **JOHNSON & JOHNSON MEDICAL LIMITED** [GB/GB]; Erskine House, 68-73 Queen Street, Edinburgh EH2 4NH (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ADDISON, Deborah** [GB/GB]; 2 Dovenanter Cottage, Keasden, Near

Clapham, Via Lancaster LA2 8HB (GB). **ESSLER, Alicia, Joanna** [GB/GB]; 17B Walton Street, Skipton, North Yorkshire BD23 2QX (GB). **CULLEN, Breda, Mary** [GB/GB]; 7 Consort Street, Skipton, North Yorkshire BD23 1HR (GB). **SILCOCK, Derek, Walter** [GB/GB]; 2 Ash Grove, Skipton, North Yorkshire BD24 1QP (GB).

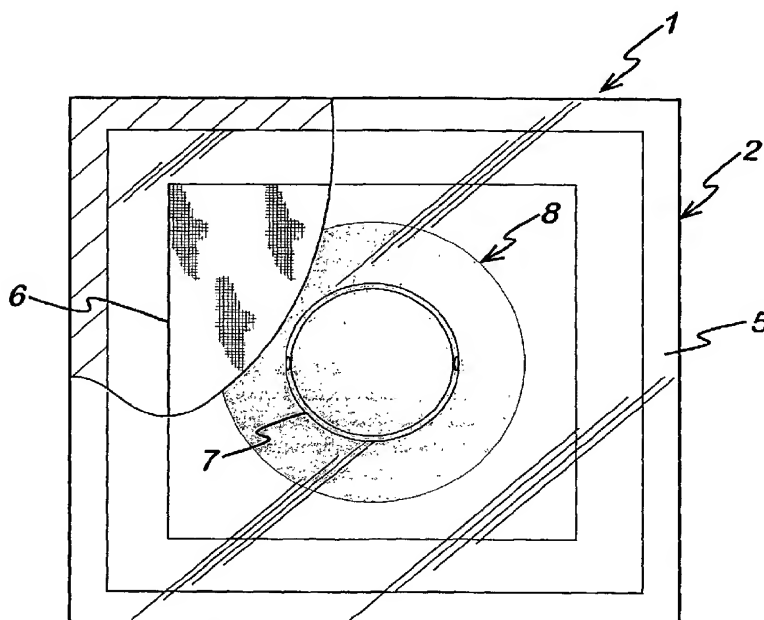
(74) Agents: **JAMES, Anthony, Christopher, W., P.** et al.; Carpmaels & Ransford, 43-45 Bloomsbury Square, London WC1A 2RA (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: WOUND TREATMENT DEVICE



(57) Abstract: A wound treatment device comprising a water-impermeable envelope having at least one aperture, wherein the envelope contains a therapeutic substance, and wherein the at least one aperture in the envelope is blocked by a material that breaks down in the presence of one or more active components of wound fluid thereby permitting the therapeutic substance to contact the wound fluid. Preferably, the aperture is blocked by a material that is a substrate for an enzyme present in wound fluid, such as a protease.

WO 2004/028423 A1



ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *with international search report*

WOUND TREATMENT DEVICE

The present invention relates to articles that can provide controlled delivery of one or more therapeutic agents to a wound.

5

The amount and composition of wound fluid (exudate) produced by a wound depends on the type of wound and the history of wound healing. For example, surgical wounds have an acute inflammatory phase of a few days during which discharge is significant, after which the rate of exudate production can be expected to fall sharply. Chronic wounds, such as ulcers, produce wound fluid containing elevated levels of protease enzymes. Infected wounds generally produce substantially more exudate than non-infected wounds, and the composition of the wound fluid is different. Burns produce large amounts of wound exudate having characteristic properties.

15

Infection of wounds by bacteria delays the healing process, since bacteria compete for nutrients and oxygen with macrophages and fibroblasts, whose activities are essential for the healing of the wound. Infection results when bacteria achieve dominance over the systemic and local factors of host resistance. Infection is therefore a manifestation of a disturbed host/bacteria equilibrium in favour of the invading bacteria. This elicits a systemic septic response, and also inhibits the multiple processes involved in wound healing. Lastly, infection can result in a prolonged inflammatory phase and thus slow healing, or may cause further necrosis of the wound. The granulation phase of the healing process will begin only after the infection has subsided.

25

Chronically contaminated wounds all contain tissue bacterial flora. These bacteria may be indigenous to the patient or might be exogenous to the wound. Closure, or eventual healing of the wound is often based on a physician's ability to control the level of the bacterial flora.

30

If clinicians could respond to wound infection as early as possible the infection could be treated topically as opposed to having to use antibiotics. This would also

lead to less clinical intervention/hospitalisation and would reduce the use of antibiotics and other complications of infection.

Current methods used to identify bacterial infection rely mainly on judgement of the odour and appearance of a wound. With experience, it is possible to identify an infection in a wound by certain chemical signs such as redness or pain. Some clinicians take swabs that are then cultured in the laboratory to identify specific organisms, but this technique takes time.

Pain is also associated with infected and chronic wounds. Biochemically, pain is experienced when there is an increase of kinins (bradykinin) in the area of the wound. Kinins are produced by the proteolytic breakdown of kininogen, and the protease responsible for this is kallikrein. Kallikrein also stimulates the production of tissue plasminogen activator (t-PA)

15

It is known to provide antimicrobial wound dressings. For example, such dressings are known having a liquid-permeable wound contacting layer, an intermediate absorbent layer and an outer, liquid-impervious backing layer, in which one or more of the layers contains an antimicrobial agent. For example, EP-A-0599589 describes layered wound dressings having a wound contacting layer of a macromolecular hydrocolloid, an absorbent layer, and a continuous, microporous sheet intermediate the wound contacting layer and the absorbent layer. The absorbent layer contains a low molecular weight antimicrobial agent that can diffuse into the wound.

25

Previous therapeutic (e.g. antimicrobial) wound dressings suffer from the drawback that the release of the therapeutic agent is relatively unresponsive to the condition of the wound being treated. This is undesirable because all unnecessary medication can interfere with the processes of wound healing. In the case of antimicrobial wound dressings, unnecessary medication can result in resistant microorganisms.

30

There is thus a need for a wound treatment device that will selectively release therapeutic agents such as antimicrobial agents and/or pain relieving agents into wounds only when there is a clinical need. Such a device could provide early intervention with suitable treatment (e.g. a topical antimicrobial treatment) before
5 severe clinical symptoms or wound chronicity sets in.

In a first aspect, the present invention provides a wound treatment device comprising a water-impermeable envelope having at least one aperture, wherein the envelope contains a therapeutic substance, and wherein the at least one
10 aperture in the envelope is blocked by a material that breaks down in the presence of one or more components of wound fluid thereby permitting the active substance to contact the wound fluid.

The term "envelope" refers to a small package or enclosure that can be inserted
15 onto or into a wound. It is preferably covered by a secondary dressing to hold it in place and provide absorbency for wound fluid. The package is substantially impermeable to liquid water until the aperture is opened by the action of one or more components present in wound fluid. The envelope outside the aperture is normally formed from a material that is substantially impermeable to wound fluid,
20 and that preferably does not break down in the presence of wound fluid. The wound fluid and/or the wound is thus not exposed to the therapeutic agent inside the envelope until the aperture is opened, and this enables the treatment to be tailored to predetermined wound conditions and unnecessary medication to be avoided. The device can be used in conjunction with a wide range of existing
25 wound dressings, and is sufficiently small that it will not interfere with the absorbency of such dressings.

In certain embodiments the envelope is formed substantially from flexible sheet material. The sheet material is usually substantially water-impermeable (it may be
30 permeable to water vapor, but not to liquid water), and suitably it is substantially non-degradable or erodible in wound fluid. In this way the walls of the envelope around the enclosure are substantially impermeable to, and unaffected by, the wound fluid. Preferably, the envelope consists essentially of such sheet material,

such as thermoplastic film, for example in the form of a sachet. Typical film thicknesses are from about 10 to about 100 micrometers. Suitable thermoplastics include polyolefins such as polyethylene, copolymers such as ethylene methyl acrylate, or fluoropolymers such as polyvinylidene fluoride. Such envelopes are
5 extremely low cost and can be made in a broad range of sizes and shapes enabling them to be applied to all types of wounds, including cavity wounds. Suitable sizes include envelopes having a maximum dimension of from about 2mm to about 200mm, for example from about 5mm to about 100mm, typically from about 10mm to about 50mm. Typical envelope configuration is a sachet
10 formed by bonding together two sheets of film material (or one sheet folded over) around a periphery. Other suitable envelopes can be made from a web or tube of sheet material on form-fill-seal equipment.

Preferably, the aperture or apertures take up only a small part of the area of the
15 envelope, since the barrier materials are generally more expensive than the sheet materials used to form the envelope. In certain embodiments, the total area of the apertures in the envelope is from about 0.01 to about 1cm². Preferably, the envelope has fewer than 10 such apertures, more preferably fewer than 5, and most preferably only one such aperture. Typically, the apertures make up from
20 about 0.1% to about 50% of the surface area of the envelope, more typically from about 1% to about 30%, and preferably from about 1% to about 10% of the surface area of the envelope.

The mean area of each aperture may for example be from about 1 to about 400
25 mm², preferably from about 2 to about 200 mm², and more preferably about 10 to about 100 mm².

The apertures in the envelope are blocked by a material that breaks down in wound fluid to open the apertures. The breakdown of the barrier material may be
30 by dissolution, or by enzymatic or other chemical degradation by the ingredients of wound fluid. In certain embodiments, the barrier material breaks down preferentially in heavily exuding wounds. In certain embodiments, the degradable material breaks down preferentially in infected wounds.

For example, the barrier material may comprise a water soluble material, such as a water soluble macromolecule. At medium to high levels of exudate the soluble material is dissolved by the exudate, thus opening the apertures. At low levels of exudate or where there is a dry wound the soluble material will stay in place so that the apertures in the device remain occluded.

Suitable soluble materials for partially or completely occluding the apertures include water soluble macromolecular materials (hydrogels) such as sodium alginate, sodium hyaluronate, alginate derivatives such as the propylene glycol alginate described in EP-A-0613692, and soluble hydropolymers formed from vinyl alcohols, vinyl esters, vinyl ethers and carboxy vinyl monomers, meth(acrylic) acid, acrylamide, N-vinyl pyrrolidone, acylamidopropane sulphonic acid, PLURONIC (Registered Trade Mark) (block polyethylene glycol, block polypropylene glycol) polystyrene-, maleic acid, NN-dimethylacrylamide diacetone acrylamide, acryloyl morpholine, and mixtures thereof. Suitable hydrogels are also described in US-A-5352508.

Other suitable materials for occluding the apertures of the device are polymeric materials that are not soluble in water, but that are bioerodible in wound fluid. Examples include polylactide/polyglycolide copolymers, oxidized regenerated cellulose, chitosan, chitin, and mixtures thereof.

Other suitable materials for partially or completely occluding the apertures of the envelope are pH-sensitive materials that are substantially insoluble in water at 25°C under acidic conditions, but substantially soluble in water at 25°C under neutral or alkaline conditions. Whilst it is no simple matter to determine the actual pH at a wound site, it appears that the pH of chronic or infected wounds is neutral or slightly alkaline, whereas the pH of intact skin is slightly acidic (pH 4 or 5).

30

Preferably, the pH-sensitive material is substantially insoluble in water at 25°C and pH 4 and substantially soluble in water at 25°C and pH 8. Preferably, the polymer becomes soluble with increasing pH at a pH in the range of 5 to 7, more preferably

5.5 to 6.5. In this context the term "soluble" preferably denotes an equilibrium solubility of the material greater than 1%w/w in water at 25°C. Particularly suitable are film-forming polymers and mixtures, such as those used to provide enteric coatings on orally administered medicaments.

5

Preferably, the pH-sensitive material comprises a polymer selected from the group consisting of cellulose derivatives, starch derivatives, pectins, polyacrylates, polyvinyl acetate phthalate, and mixtures thereof.

10 Preferred cellulose derivatives are selected from cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, oxidised regenerated cellulose, and mixtures thereof.

15 Preferred polyacrylates are selected from the copolymers of methacrylic acid with methyl methacrylate. Particularly preferred are various copolymers of this type sold under the Registered Trade Mark EUDRAGIT. By varying the ratio of methacrylic acid to methyl methacrylate it is possible to control the pH at which these copolymers dissolve in order to optimise the properties of the material.

20

In yet other embodiments, the degradable material occluding the aperture comprises a substrate for an enzyme present in wound fluid.

For example, it has been discovered that wound fluid from infected wounds, and
25 from wounds that are apparently not clinically infected but which go on to become infected within a few days, have high levels of neutrophil elastase activity and may also have high levels of other inflammatory enzymes, such as macrophage proteases, other neutrophil proteases, bacterial collagenase, plasmin, hyaluronidase, kallikrein or t-PA. It is also known that the wound fluid produced by
30 chronic wounds such as diabetic ulcers, decubitis ulcers or venous ulcers, have elevated levels of protease enzymes. Hence, the use of enzyme substrates enables the properties of the devices according to the present invention to be responsive selectively to wound infection and wound chronicity.

Preferred enzyme substrates for use in the degradable material comprise a substance selected from the group consisting of elastin, fibronectin, collagen, crosslinked gelatin, fibrinogen, casein, hyaluronic acid, plasminogen, fibrin, chitin, 5 chitosan, oxidized cellulose, polylactide/polyglycolide copolymers, and mixtures thereof.

In preferred embodiments, the materials for partially or completely occluding the apertures of the envelope comprise substrate materials for one or more protease 10 enzymes present in wound fluid, especially infected wound fluid. Such proteases include elastase, collagenase, pectinase, matrix metalloproteinases, and mixtures thereof. Preferred substrate materials include substances selected from the group consisting of elastin, fibronectin, collagen, crosslinked gelatin, fibrinogen, casein, hyaluronic acid, plasminogen, fibrin, and mixtures thereof.

15

The barrier composition may comprise at least 25%, more preferably at least 50% w/w based on the weight of the composition of the soluble macromolecular materials, pH-sensitive materials, or substrate materials on a dry weight basis. The barrier composition may further comprise from about 5 to about 50% by weight, 20 preferably from 15 to 40% by weight, on the same basis of one or more humectants and/or plasticisers such as glycerol, sorbitol or polyethylene glycol.

The one or more therapeutic agents may be any substance suitable for the treatment of wounds. In certain embodiments the therapeutic agents are selected 25 from the group consisting of antiseptics, antibiotics, analgesics, steroids and growth factors. Preferred therapeutic agents are antimicrobial agents including metallic silver, silver salts and compounds such as silver sulfadiazine, povidone iodine, chlorhexidine and mixtures thereof, and analgesic agents including benzocaine, lidocaine and mixtures thereof.

30

The therapeutic agent may be present in the envelope in particulate or soluble or otherwise dispersible form, so that it can pass out of the envelope into the wound once the aperture is opened by the action of wound fluid. In other embodiments,

the therapeutic agent may be retained inside the envelope even after the aperture has opened, for example by being dispersed in or on a substrate that is too large to fit through the aperture. An example would be a silver treated cloth.

- 5 In certain embodiments the therapeutic material inside the envelope is adapted to provide sustained release of the therapeutic agent in wound fluid. For example, the material may comprise a bioerodible substance having the therapeutic agents dispersed or encapsulated therein. Suitable bioerodible substances include proteins such as albumin, collagen, cross-linked gelatin or zein, polysaccharides
10 such as oxidized regenerated cellulose, biodegradable synthetic polymers such as polylactate/polyglycolate copolymers, glycosaminoglycans such as hyaluronate, and mixtures thereof.

- In certain embodiments, the therapeutic material may be dispersed in or on
15 particles suitable for drug delivery. The particles may be made by any suitable technique, including comminution, coacervation, or two-phase systems for example as described in US-A-3886084. Techniques for the preparation of medicated microspheres for drug delivery are reviewed, for example, in Polymeric Nanoparticles and Microspheres, Guiot and Couvreur eds., CRC Press (1986).
20 The microparticles are preferably loaded with from 1 to 90 wt.%, more preferably from 3 to 50 wt.% of the therapeutic agents.

- Preferably, the wound treatment device according to the present invention is sterile and packaged in a microorganism-impermeable container.
25

In a second aspect, the present invention provides a wound dressing comprising a wound treatment device according to the present invention.

- In a third aspect, the present invention provides a method of treatment of a wound
30 comprising applying thereto a device according to the present invention. Preferably, the method further comprises applying a wound dressing over the device.

An embodiment of the present invention will now be described further, by way of example, with reference to the accompanying drawings, in which:

Figure 1 shows a perspective view partially cut away of a wound treatment device according to the invention; and

- 5 Figure 2 shows a longitudinal cross-sectional view of the dressing of Fig. 1.

Example 1

Referring to Figure 1, the wound treatment article 1 comprises an envelope 2 of
10 substantially liquid-impermeable sheet material. The envelope consists of front
and back faces 3,4 of a continuous polypropylene film that are heat bonded
around their and edge margin 5 to form a waterproof sachet. Inside the envelope
there is a rectangular sheet 6 of silver-impregnated antimicrobial cloth. The
envelope comprises an aperture 7 occluded by a collagenase-degradable film
15 composition 8

The device is prepared as follows. 1g of collagen fibers formed by freeze drying
Type I collagen extracted from limed bovine hide were suspended in 100ml of
0.05M acetic acid. This suspension was poured into a plastic dish to a thickness
20 of 4mm. The dish was placed in a drying cabinet at room temperature until the
weight of the suspension had reduced to 50% of the initial weight. At this stage
the apertured polymer sheet that will form the apertured face 3 of the envelope
was placed on the surface of the collagen suspension. The suspension was then
fully dried and peeled from the square dish. The resulting material has the
25 aperture of the sheet occluded by a thin film of Type I collagen. The apertured
sheet 3 with the layer of collagen 8 applied thereto was then assembled into the
device by heat bonding to the back sheet 4, with the antimicrobial cloth inserted
between the sheets 3 and 4.

30 The device is packaged in a microorganism-impermeable pouch (not shown), and
sterilised using gamma radiation.

In use, the device 1 is removed from the package, and the article is applied to the wound and held in place by a sterile and absorbent secondary dressing. The dissolution of the collagen contained in the barrier layer 8 in the presence of elevated levels of collagenase exposes the wound fluid to the antimicrobial silver cloth inside the envelope in response to increased collagenase production by infected or chronic wounds.

Example 2

10 In another embodiment, the barrier layer 8 contained chitosan as the biodegradable component. The chitosan containing film composition prepared as follows.

100.0 grams of chitosan chloride was mixed in 1.5 liters of water until blended.
15 200.0 grams of glycerol were blended into the mixture, after which 200.0 grams of polyethylene glycol ("PEG") were then added. The resulting mixture was then filtered and coated over the aperture as described in Example 1. The mixture was then frozen and freeze dried, or air dried in circulating air at room temperature.

20 The above embodiments have been described by way of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

CLAIMS

1. A wound treatment device comprising a water-impermeable envelope having at least one aperture, wherein the envelope contains a therapeutic substance, and wherein the at least one aperture in the envelope is blocked by a degradable material that breaks down in the presence of one or more components of wound fluid thereby permitting the therapeutic substance to contact the wound fluid.
2. A wound treatment device according to claim 1, wherein the envelope is formed substantially from flexible sheet material.
3. A wound treatment device according to claim 1 or 2, wherein the total area of the apertures in the envelope is from about 0.01 to about 1cm².
4. A wound treatment device according to claim 1, 2 or 3, wherein the envelope has only one said aperture.
5. A wound treatment device according to any preceding claim, wherein the degradable material breaks down preferentially in infected wounds.
6. A wound dressing according to any preceding claim, wherein the degradable material comprises a substrate for an enzyme present in wound fluid.
7. A wound treatment device according to any preceding claim, wherein the degradable material comprises a substance selected from the group consisting of elastin, fibronectin, collagen, crosslinked gelatin, fibrinogen, casein, hyaluronates, plasminogen, fibrin, chitin, chitosan, oxidized cellulose, polylactide/polyglycolide copolymers, and mixtures thereof.
8. A wound treatment device according to any preceding claim wherein the therapeutic agents are selected from the group consisting of antiseptics, antibiotics, analgesics, steroids and growth factors, and mixtures thereof.

9. A wound treatment device according to claim 8, wherein the therapeutic agents comprise an antimicrobial agent selected from colloidal silver, silver sulfadiazine, povidone iodine, chlorhexidine, and mixtures thereof.

5

10. A wound treatment device according to any preceding claim, wherein the device is adapted to provide sustained release of the therapeutic agent into the wound fluid following the opening of the aperture.

10 11. A wound treatment device according to any preceding claim, wherein the therapeutic substance is dispersed in or on a solid substrate

12. A wound treatment device according to any preceding claim, wherein the therapeutic agent is dispersed or encapsulated in a bioerodible substance.

15

13. A wound treatment device according to claim 12, wherein the bioerodible substance is selected from the group consisting of proteins, polysaccharides, biodegradable synthetic polymers, glycosaminoglycans, and mixtures thereof.

20 14. A wound treatment device according to any preceding claim which is sterile and packaged in a microorganism-impermeable container.

15. A wound dressing comprising a wound treatment device according to any preceding claim.

25

1/1

Fig. 1

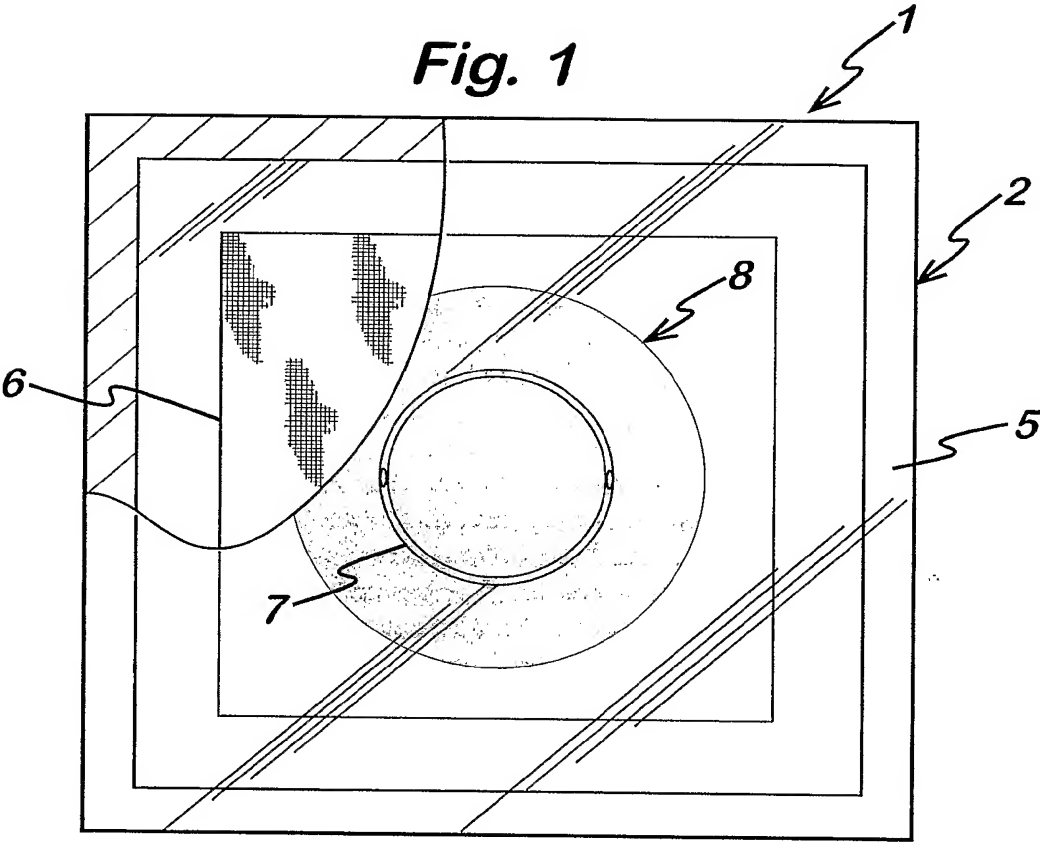
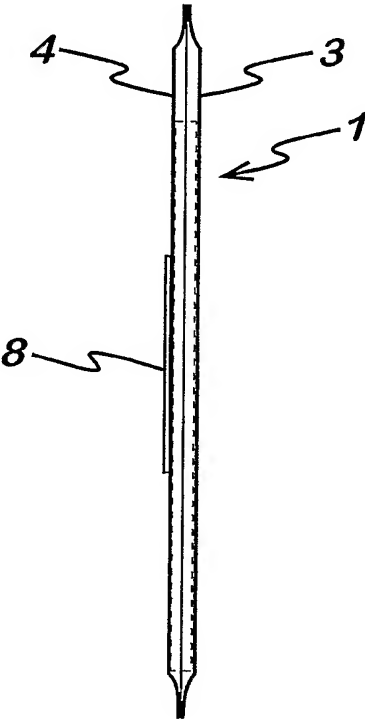


Fig. 2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/04118

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61F13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 369 997 A (JOHNSON & JOHNSON MEDICAL LTD) 19 June 2002 (2002-06-19) page 13, line 1 - line 2 page 3, line 30 -page 4, line 6 page 4, line 21 - line 29 page 10, line 28 -page 11, line 6 page 13, line 4 - line 6 page 13, line 20 - line 32	1,2,5, 7-9,11, 14,15
Y		3,4,6, 10,12,13
Y	US 4 499 896 A (HEINECKE STEVEN B) 19 February 1985 (1985-02-19) column 4, line 43 - line 45; claims 1-5; example 10 --- -/--	3,4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

8 December 2003

Date of mailing of the international search report

18/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Douskas, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/04118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 160 200 A (EHRNSPERGER BRUNO J ET AL) 12 December 2000 (2000-12-12) column 2, line 13 - line 31 column 3, line 27 - line 33 column 11, line 38 - column 12, line 15 column 13, line 49 - line 59; claims 1-20 ---	6
Y	US 5 549 908 A (SMITH DANIEL J ET AL) 27 August 1996 (1996-08-27) column 11, line 62 - line 67; claims 1,22-26 ---	10,12,13
P,X	GB 2 379 392 A (JOHNSON & JOHNSON MEDICAL LTD) 12 March 2003 (2003-03-12) the whole document ---	1-5,9, 11,14,15
P,X	WO 03 026544 A (CULLEN BRED A MARY ; JOHNSON & JOHNSON MEDICAL LTD (GB); KIRKWOOD AN) 3 April 2003 (2003-04-03) the whole document ---	1-15
A	WO 02 38097 A (JOHNSON & JOHNSON MEDICAL LTD ; ADDISON DEBORAH (GB); SILCOCK DEREK) 16 May 2002 (2002-05-16) the whole document ---	1-5, 8-10,14, 15
A	US 4 541 426 A (WEBSTER DAVID F) 17 September 1985 (1985-09-17) claims; figures ---	1
A	EP 0 875 222 A (JOHNSON & JOHNSON MEDICAL) 4 November 1998 (1998-11-04) claims; figures ---	1
A	US 6 143 037 A (BONADIO JEFFREY F ET AL) 7 November 2000 (2000-11-07) column 3, line 1 - line 16; claims ---	10-13
A	US 5 540 922 A (FABO TOMAS) 30 July 1996 (1996-07-30) claims -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/04118

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2369997	A	19-06-2002	AU 2216102 A EP 1341561 A1 WO 0247737 A1	24-06-2002 10-09-2003 20-06-2002
US 4499896	A	19-02-1985	AU 553597 B2 AU 1292783 A BR 8301619 A CA 1193966 A1 DE 3365233 D1 EP 0090564 A2 ES 279098 U ES 280978 U ES 284681 U JP 1625184 C JP 2052505 B JP 58180152 A MX 157855 A NZ 203745 A ZA 8302238 A	24-07-1986 06-10-1983 06-12-1983 24-09-1985 18-09-1986 05-10-1983 01-01-1985 16-10-1985 01-11-1985 18-11-1991 13-11-1990 21-10-1983 16-12-1988 20-02-1987 28-12-1983
US 6160200	A	12-12-2000	AU 4850399 A BR 9911323 A CA 2333874 A1 CN 1126526 B EP 1094775 A2 JP 2002519101 T TW 406014 B WO 0000119 A2 US 6410821 B1 ZA 200006956 A	17-01-2000 20-03-2001 06-01-2000 05-11-2003 02-05-2001 02-07-2002 21-09-2000 06-01-2000 25-06-2002 14-08-2001
US 5549908	A	27-08-1996	WO 9427647 A1	08-12-1994
GB 2379392	A	12-03-2003	NONE	
WO 03026544	A	03-04-2003	GB 2380135 A WO 03026544 A1	02-04-2003 03-04-2003
WO 0238097	A	16-05-2002	AU 1255202 A EP 1333788 A1 WO 0238097 A1	21-05-2002 13-08-2003 16-05-2002
US 4541426	A	17-09-1985	AT 27904 T AU 564402 B2 AU 2644984 A CA 1214085 A1 DE 3464326 D1 EP 0122085 A1 JP 1036380 B JP 1555629 C JP 59205959 A ZA 8402504 A	15-07-1987 13-08-1987 11-10-1984 18-11-1986 30-07-1987 17-10-1984 31-07-1989 23-04-1990 21-11-1984 30-01-1985
EP 0875222	A	04-11-1998	GB 2324732 A ,B US 5981822 A AT 221360 T AU 748103 B2 AU 6375598 A	04-11-1998 09-11-1999 15-08-2002 30-05-2002 05-11-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/04118

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0875222	A		CA 2236436 A1	02-11-1998
			DE 69806842 D1	05-09-2002
			DE 69806842 T2	09-01-2003
			EP 0875222 A1	04-11-1998
			JP 11056900 A	02-03-1999
US 6143037	A	07-11-2000	AU 715339 B2	20-01-2000
			AU 3386697 A	07-01-1998
			CA 2257976 A1	18-12-1997
			EP 0910301 A1	28-04-1999
			JP 2000512519 T	26-09-2000
			WO 9747254 A1	18-12-1997
US 5540922	A	30-07-1996	SE 500973 C2	10-10-1994
			CA 2132983 A1	14-10-1993
			DE 69305735 D1	05-12-1996
			DE 69305735 T2	06-03-1997
			EP 0633758 A1	18-01-1995
			ES 2093420 T3	16-12-1996
			JP 7505310 T	15-06-1995
			SE 9200984 A	01-10-1993
			WO 9319710 A1	14-10-1993